REMARKS

Claims 11, 12, 14-17 and 19-23 are pending in the Subject Application. Claims 11, 12, 14-17 and 19-23 have been cancelled, and new claims 24-29 have been added. Support for the claims, is found *inter alia* in the specification and examples herein, and in particular in the specification at page 2 lines 28-31 and page 28, lines 22-25. None of the amendments made herein constitute the addition of new matter.

Applicants thank the Examiner for withdrawing his objection to claims 11, 12, 14-17 and 19-23 under 35 U.S.C. § 103 as being unpatentable over US Patent No. 5,763,416, or WO 96/39431, in view of US Patent No. 5,645,084, US Patent No. 5,700,774 and US Patent No. 6,048,964.

REJECTION UNDER 35 U.S.C. § 103:

In the Office Action, the Examiner provided a new rejection for claims 11, 12, 14-17 and 19-23 under 35 U.S.C. § 103 as allegedly being unpatentable over Ahrens et al, in view of US Patent No. 5,763,416 and US Patent No. 6,048,964. The Examiner asserted that based on Ahrens et al, in view of US Patent No. 5,763,416 and US Patent No. 6,048,964, it would have allegedly been obvious to one of ordinary skill in the art to combine to make the claimed invention, that of preparing ex-vivo cultured progenitor cells transformed with BMP-2 for implantation at a site of a bone infirmity.

In response, Applicants traverse the rejection of claims 11, 12, 14-17 and 19-23 under 35 U.S.C. § 103. Applicants maintain that Ahrens et al, in view of US Patent No. 5,763,416 and US Patent No. 6,048,964, do not render the instant invention obvious, nor would a person of ordinary skill in the art have had a reasonable and/or credible expectation of success in obtaining the instant claimed invention given the teachings of Ahrens et al, in view of US Patent No. 5,763,416 and US Patent No. 6,048,964.

Applicants maintain that it would not have been obvious to obtain Applicants' invention, *a priori*, based on the cited references. It would not be expected for a method of *in vivo* gene transfer of a BMP sequence or in vitro transformation of a cell with BMP-2 to teach:

> "A method of inducing functional bone formation at a site of bone infirmity in a human, comprising the steps of:
>
> (d) transforming a cultured mesenchymal stem cell with a DNA encoding bone morphogenesis protein 2 (BMP-2);
>
> (e) culturing the cultured mesenchymal stem cell transformed in step (a), under conditions enabling expression of said DNA encoding bone morphogenesis protein 2; and
>
> (f) implanting said cultured mesenchymal stem cell at a site of bone infirmity
>
> whereby autocrine and paracrine effects of expressed bone morphogenesis protein 2 result in functional bone formation at said site of bone infirmity, thereby inducing functional bone formation at a site of bone infirmity" (claim 24).

Ahrens et al., describes the transformation of a mesenchymal progenitor cell line with BMP-2 or BMP-4, and, following the addition of the osteoinductive compounds, ascorbic acid and β-glycerophosphate show ***in vitro*** differentiation of the treated cells into 3 different mesenchymal lineages, among which one is bone. Ahrens fails to demonstrate *in vivo* bone induction, and moreover, the methods taught by Ahrens are not **specific** to bone induction due to BMP-2, since other osteoinductive compounds were administered concurrently. Further, since Ahrens discloses *in vitro* methods alone, autocrine and paracrine effects of the expressed BMP on bone formation by a transfected mesenchymal stem cell implanted at a site of infirmity could not be evident, nor anticipated to one skilled in the art.

Success of recombinant protein administration, *in vivo* gene transfer or *in vitro* transformation of a stem cell with BMP-2, does not predicate success of implantation of ex-vivo cultured cells, and formation of enhanced, functional bone formation and therefore obtaining similarly beneficial results is not an expected and obvious outcome.

Evidence that one skilled in the art would not have found it obvious to obtain the instant invention was submitted in the Declaration provided in the communication dated March 6, 2003, which states, *inter alia* that "direct in vivo gene transfer is not predictive a priori for use of ex vivo engineered cells for implantation for bone repair, and therefore obtaining credible and/or functional results is not a priori an expected and or obvious outcome" and that "it would not have been obvious that a person of ordinary skill in the art would have had a reasonable expectation of success in the producing of the instant invention given the teachings of Bonadio in combination with He, McKay and/or Hattersley".

Failing direct experimental evidence, none of the cited references had an ability to reveal enhanced bone repair, as a result of the participatory action of both autocrine and paracrine mechanisms as a consequence of implantation of ex-vivo cultured BMP-transformed cells. Thus, the cited references provide no opportunity, hence no ability to teach or anticipate the enhanced, directed, superior repair as a result of participatory autocrine and paracrine effects of implantation of ex-vivo cultured cells genetically engineered to express BMP-2.

In addition, the unexpected results of a higher efficiency of the extent of bone regeneration, and a more organized deposition along fracture edges were due to the participatory effects mediated by the autocrine and paracrine mechanisms involved (See Declaration), thus the instant invention would not be obvious to one of ordinary skill in the art.

Therefore, Ahrens, Bonadio and Lee in combination do not render the methods of the instant invention obvious. The combined references do not teach, or render obvious, a method for inducing functional bone formation at a site of bone infirmity in a human via implantation of transfected ex-vivo cultured mesenchymal stem cells, where autocrine and paracrine effects of expressed bone morphogenesis protein 2 result in functional bone formation at the site of bone infirmity.

In addition, the Examiner has also rejected claims 11, 12, 14-17 and 19-23 in view of the above cited references, further in view of Wozney, under 35 USC 103.

Wozney teaches the utility of expressing a BMP receptor for BMP-2 in cells responding to the growth factor. Applicants maintain, by reasoning disclosed hereinabove, that the previously cited references do not render obvious the methods of inducing functional bone formation via implanting ex-vivo cultured MSC transfected with BMP-2. Since the methods are not obvious in view of the art, neither is MSC expression of a BMP-2 receptor. Therefore, Applicants submit that the additional reference does not render the instant invention obvious.

In addition the Examiner rejected claims 11, 12, 14-17 and 19-23 in view of the above cited references, further in view of Hattersley, under 35 USC 103. Hattersley teaches the use of PTH and its receptor in the context of BMP-2. Applicants similarly maintain, by reasoning disclosed hereinabove, that the previously cited references do not render obvious the methods of inducing functional bone formation via implanting ex-vivo cultured MSC transfected with BMP-2. Since the methods are not obvious in view of the art, neither is MSC expression of a PTH/PTH receptor. Therefore, Applicants submit that the additional reference does not render the instant invention obvious.

Accordingly, Applicants request the Examiner to reconsider and withdraw the rejection of the claims under 35 U.S.C. 103.

Based on the foregoing, the pending claims are deemed to be allowable. Their favorable reconsideration and allowance is respectfully requested. Should the Examiner have any question or comment as to the form, content or entry of this Amendment, the Examiner is requested to contact the undersigned at the telephone number below.

The undersigned Attorney hereby authorizes the United States Patent and Trademark Office to charge Deposit Account No. 05-0649 for any fees required.

Respectfully Submitted,

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